August 31, 1965

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Dear Doctor McGill:

We have recently noted some publicity in the papers concerning a project to teach baboons to smoke cigarettes. We would be interested in learning a little more about these studies - whether they are entirely preliminary or exploratory or part of an extensive plan.

Our own smoke inhalation studies so far have involved only mice, rats, hamsters and dogs. The exposure of these small animals by the inhalation route involves many problems. The smoke has to be generated by mechanical means, keeping the conditions of combustion close to those used by humans in normal smoking. The smoke has to be diluted with the proper proportion of air and delivered to the lung surfaces at the right age, in seconds or fractions thereof, following generation at the burning zone. These problems might be simplified in the case of an animal capable of smoking in the manner of humans, but of course other problems arise such as number of animals, housing, costs etc.

A special problem with the smaller animals is that the smoke really ought not to be allowed to pass through the nasal passages which may filter out a substantial proportion of the particulate matter so that it does not reach the lung at all. Most of the work with these species so far has involved nasal inhalation.

Still another important problem that includes both man and baboon is to devise a method of measuring the actual exposure of lung surfaces to total smoke. The number of cigarettes lighted up in a day by a human smoker (as deduced from questionnaires) is not a very good measure of lung exposure because of variations in the numbers of puffs actually taken and the depth of inhalation, if any. For this reason, we have been endeavoring to develop a physiological or biochemical method of monitoring or estimating the actual lung exposure.

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The most promising method so far is the measurement of blood carbon monoxide. This gas is present in a small but fairly constant concentration in cigarette smoke. The evidence is that it is little absorbed through the tissues of the oral area, but is avidly absorbed through the alveolar membranes. Since humans can puff by the stop-watch, and inhale or not as directed, we have been able to start at standardizing the blood-CO response to regulated smoking procedures. Although carbon monoxide is eventually eluted from

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the blood again, this process, unlike the metabolism of nicotine, is slow enough so that analytical work can be carried out comfortably without undue danger of confusion in the results attributable to changes during the time between exposure and sampling.

After sufficient standardization, we hope that we can use blood sampling more or less routinely as a method of checking subject questionnaire data on numbers of cigarettes smoked (or rather burned) per day. Discrepancies between numbers lighted and amounts of smoke actually inhaled may be quite instructive with respect to nervous habits, for example. A man who lights a large number of cigarettes but takes few real puffs may be quite a different kind of person from one who lights relatively few but really smokes them. Inhalers may be quite different from non-inhalers and we doubt whether subjects can ordinarily judge very well whether they inhale or not, all aside from any emotional factors that may prejudice what they say they do.

I think that in humans carbon monoxide absorption may be a fairly good indicator of lung surface exposure to whole smoke, including particulate matter. While there must be some loss of particulates in the mouth, throat and larynx as the aerosol passes through to the lung, this should be reasonably nearly constant in humans. It may not be the same for rats, mice and hamsters if these breathe through the nose. The fraction of the original particulate matter which reaches the lung may be considerably lower in these animals, if they breathe the smoke in through the nasal passages, as they generally have done in the experiments carried out in the past. The fraction might well be fairly constant in this case also, but constant at a lower level in relation to the carbon monoxide reaching the alveolar. The same blood analysis might be used with the small animals, if once a method of standardization could be carried out by use of some marker present only in the particulate matter. Nicotine is probably not a good one because of its rapid absorption and metabolism, though Harris and Negroni have used determinations of nicotine in mouse lungs as a qualitative indication that some particulate matter is reaching this organ.

In any case, if extensive experiments are to be done with baboons, the question of the extent of exposure of the lung tissues is likely to arise again if any effort to observe dose-response relationships is to be made, as it certainly must sooner or later.

A progress report on one of the human studies is being enclosed for your information. It should, of course, be regarded as confidential and not cited as such until published.

With kind regards and all best wishes,

Sincerely yours,

Robert C. Hockett, Ph.D.
Associate Scientific Director

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